PET-Derived Biodistribution and Dosimetry of the Benzodiazepine Receptor-Binding Radioligand ^{11}C -(R)-PK11195 in Children and Adults

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The PET tracer ^{11}C -(R)-PK11195 (PK) is an antagonist of the peripheral-type benzodiazepine binding site and allows the non-invasive imaging of microglial activation seen in several neurologic disorders affecting the mature and developing brain. The objective of this study was to derive the biodistribution and in vivo radiation dose estimates of PK in children studied for brain inflammatory conditions and in healthy adults. **Methods:** Twenty-two children (mean age $\pm$ SD, 9.5 ± 4 y; range, 4–17 y; 10 girls) who underwent dynamic PK PET for conditions involving brain inflammation were studied. Seven healthy adults (age, 27.4 ± 7.5 y; range, 22–41 y; 3 women) were evaluated using the same protocol. Normal-organ time-activity curves and residence times were derived and absorbed doses then calculated using the OLINDA software. Two other healthy young adults (1 man, 1 woman) also underwent sequential whole-body PET using a PET/CT scanner to obtain corresponding CT images and PK pharmacokinetics. **Results:** PK uptake was highest in the gallbladder and urinary bladder, followed by the liver, kidney, bone marrow, salivary gland, and heart wall, with minimal localization in all other organs including normal brain and lungs. PK was excreted through the hepatobiliary and renal systems. The average effective dose equivalent was 11.6 ± 0.6 $\mu\text{Sv}/\text{MBq}$ (mean $\pm$ SD) for young children (age, 4–7 y), 7.7 ± 1.0 $\mu\text{Sv}/\text{MBq}$ for older children (age, 8–12 y), 5.3 ± 0.5 $\mu\text{Sv}/\text{MBq}$ for adolescents (age, 13–17 y), and 4.6 ± 2.7 $\mu\text{Sv}/\text{MBq}$ for adults. The gallbladder wall received the highest radiation dose in children younger than 12 y, whereas the urinary bladder wall received the highest dose in older children and adults. For an administered activity of 17 MBq/kg (0.45 mCi/kg), the effective dose equivalent was about 5 mSv or below for all age groups. **Conclusion:** At clinically practical administered activities, the radiation dose from ^{11}C -PK11195 in both children and adults is comparable to that from other clinical PET tracers and diagnostic radiopharmaceuticals in routine clinical use.

Key Words: biodistribution; dosimetry; ^{11}C -PK11195; PET; children

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Neuroinflammation, mediated by activated microglia, occurs in a variety of neurologic disorders and plays a role in both neuronal remodeling and plasticity after brain injury (1). Activated microglia express the peripheral benzodiazepine receptor (PBR), which is a heterooligomeric complex comprising the voltage-dependent anion channel and the adenine nucleotide carrier and is usually located in ependymal cells lining the ventricles, olfactory bulb, choroid plexus, and glial cells including astrocytes and microglia (2). However, after central nervous system injury or in cases of neurodegenerative disorders, the expression of PBRs is increased mostly in microglia, with lower or insignificant contributions from astrocytes (3). Outside the brain, PBRs are found in many peripheral organs such as the adrenal gland (particularly the cortex), salivary glands, nasal epithelium, testis, lymphoid cells, macrophages, red blood cells, thymoma cells, distal convoluted tubules, ascending loop of Henle, hepatocytes, biliary epithelial cells, and myocytes (4). Although PBRs are located primarily on the outer membrane of mitochondria, they have also been shown to be localized in the plasma membrane of the adrenal gland, testis, Leydig cells, and red blood cells (which do not have mitochondria) (5).

The PET tracer ^{11}C -PK11195 (PK), or 1-(2-chlorophenyl)- N - ^{11}C -methyl- N -(1-methylpropyl)-3-isoquinoline carboxamide, has been developed as a specific ligand for the PBR, and several studies have shown increased PK localization in a wide variety of neurologic diseases. In

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these cases, PK PET may increase our understanding of the pathophysiology of these disorders and may lead to the development of new therapeutic options. PET using PK not only may allow the noninvasive detection of neuroinflammation but also may help in the monitoring of disease progression noninvasively, both in the absence of and after treatment. However, considering the widespread distribution of PBRs in the body, determination of the biodistribution of the PK tracer is important to assess the radiation absorbed dose from PK PET. The objective of this study was to examine the biodistribution of ^{11}C -(R)-PK11195 in children and adults and determine normal organ-absorbed doses.

MATERIALS AND METHODS

Subjects

We studied 22 children (mean age $\pm$ SD, 9.5 ± 4 y; range, 4–17 y; 10 girls) who underwent dynamic PET using the Siemens Exact HR PET scanner for disorders involving brain inflammation. Children were divided into the following 3 groups, according to their age: young children (4–7 y, $n = 8$), older children (8–12 y, $n = 9$), and adolescents (13–17 y, $n = 5$). In addition, 7 young healthy adults (mean age $\pm$ SD, 27.4 ± 7.5 y; range, 22–41 y; 3 women) were scanned using the same protocol. Two other healthy young adults (1 man, 1 woman) also underwent sequential whole-body PET using a GE Discovery PET/CT scanner to obtain corresponding CT images and PK pharmacokinetics. All studies were performed in accordance with guidelines stipulated by the Human Subjects Research Committee of Wayne State University, and written informed consent was obtained from adult subjects and the parents or guardians of children. Written assent was obtained for children over the age of 7 y.

PET Procedure

The PK tracer was produced at Children's Hospital of Michigan using a synthesis module designed and built in-house (6). Both the radiochemical and chemical purities of the product were greater than 98%. The specific activity of ^{11}C -(R)-PK11195 was 47.2 ± 6.4 GBq/ μmol at the end of synthesis and 37.2 ± 4.8 GBq/ μmol at the time of administration. PET studies were performed using the CTI/Siemens EXACT/HR whole-body positron tomograph after 6–8 h of fasting. Before tracer injection, two 15-min transmission scans were acquired to correct for photon attenuation, one for the brain and the other for the torso (body) at the level of the liver or the urinary bladder. Coinciding with the tracer (17 MBq/kg) injection, a dynamic image sequence was initiated, alternating between the brain (0–20, 30–40, and 50–60 min) and the torso (20–30, 40–50, and 60–70 min), with 60-s periods interleaved for patient repositioning (Fig. 1). Torso imaging was performed at the level of liver, starting from the sixth rib (around nipples), in such a way that the heart and lower lobes of the lungs were included in the field of view (16 cm). In each age group, 2 subjects were scanned at the level of the urinary bladder instead of the liver, starting below the umbilicus. As a result, some organs—such as the lungs, heart, and intestines—were only partially included in the field of view, depending on the age and length of the subject. Although it is difficult to quantify the exact percentage represented in the region of interest (ROI), because of different subject sizes, approximately one fourth of the lungs and

FIGURE 1. Interleaved PET protocol used for acquisition of dynamic PET scan. Short 1-min interval was used to reposition patient between 2 bed positions. Subset of patients was scanned at level of urinary bladder instead of liver.

two thirds of the heart were usually included in the ROIs. Emission data were acquired in 3-dimensional mode, and measured attenuation corrections and scatter and decay corrections were applied to all PET images. In 2 adults, 3 sequential whole-body scans from head to thigh (5 bed positions, each of 4-min duration) were obtained in 3-dimensional mode using the GE Discovery STE PET/CT scanner. The PET scan was preceded by the CT scan of the same area, which was used both for attenuation correction and organ localization. Pulse oximetry, heart rate, respiratory rate, and temperature were monitored throughout the study.

PET Image Processing and Analysis

ROIs around various organs were defined manually in the brain sequence in summed images from 30 to 60 min and in the torso sequence in summed images from 40 to 70 min. Subsequently, corresponding time-activity curves were generated, and the decay-correction was negated by multiplying the activity in each image frame with $\exp(-\lambda t)$, where λ is the decay constant for ^{11}C (2.08 h^{-1}), and t is the midscan time of each frame. This procedure resulted in non-decay-corrected time-activity curves for various organs. Continuation of the time-activity curve for each region after the last time point and up to 120 min after injection was based on the physical decay of the tracer only (i.e., was calculated physically without taking biologic decay or elimination into consideration). The residence time for each organ was then calculated as the integral under the non-decay-corrected time-activity curve normalized to the injected activity and multiplied by the result with the age-specific reference man organ mass (7). No analytic function was fitted to the data points, and numeric integration was applied to obtain the area under the curves.

The residence time of the remainder activity (assumed to be homogeneously distributed in the body) was accounted for by subtracting the sum of all considered organ residence times from the inverse of the decay constant for ^{11}C (0.48 h^{-1}). We assumed no biologic elimination (i.e., excretion) of ^{11}C , because no additional data regarding tracer elimination were available. Subsequently, these residence times were used in the OLINDA software (8) to calculate effective dose equivalent (EDE), a stochastic measure of the overall detriment of radiation exposure to a person. To determine the urinary bladder wall and the gastrointestinal tract-absorbed dose estimates, we applied the voiding bladder model as included in the OLINDA software. We assumed a fast fraction (2/3) with a 20-min half-life and

a slow fraction (1/3) with a 60-min half-life. In addition, the bladder-voiding interval was set to 60 min.

Statistical Analysis

Values were expressed as mean and SD. A mixed-design repeated measures ANOVA was used to assess the effect of sex on residence times and EDE across different age groups. Moreover, a Mann–Whitney test was performed to assess any difference in pre- and post-PET scan hematologic and biochemical profiles. A *P* value of less than 0.05 was considered as significant. The SPSS program (version 16.0; SPSS Inc.) was used for the statistical analyses.

RESULTS

The time-dependent distribution of PK in the body is shown in Figures 2A–2C. Immediately after the injection, PK was most prominently taken up by the liver and heart wall and, to a lesser extent, by the salivary gland, red marrow, stomach wall, thyroid gland, and spleen. Subsequently, the activity increased in the red marrow and salivary glands, with persisting tracer uptake in the liver, heart wall, and stomach wall. PK also began to accumulate in the gallbladder, pelvis of the kidney, urinary bladder, and stomach lumen (probably from salivary and gastric secretion). Over time, PK cleared from most of the organs and finally, after about 1 h after injection, most of the remaining activity was concentrated in the 2 main excretory organs—the gallbladder and urinary bladder. Lungs showed minimal PK uptake throughout the study period. The brains in healthy adults showed low uptake and rapid washout. Some of the brains of the children (*n* = 11) also showed low uptake.

Figure 3A shows representative decay-corrected time–activity curves for the pelvis of the kidneys, liver, brain, urinary bladder, and gallbladder in a 5-y-old child with low brain uptake. There was a fast initial uptake of tracer activity in the liver and the pelvis of the kidneys, subsequently reaching a constant level. In contrast, there was a steady increase of tracer activity in both the gallbladder and the urinary bladder during the initial 60 min after tracer injection. Finally, tracer activity in the brain reached a maximum within the first 2 min and then decreased exponentially. Non–decay-corrected time–activity curves of the same organs are shown in Figure 3B. These curves were extrapolated to 240 min (12 half-lives), applying only physical decay of the tracer, and were subsequently used to calculate the cumulated activity for each organ.

Table 1 shows the calculated residence times derived from PET for the various age groups. Radiation doses, calculated from these residence times, are reported in Table 2; Table 3 summarizes the EDE in each age group. Both the EDE and the organ doses per unit injected activity decreased with age. The administration of a 17 MBq/kg (0.45 mCi/kg) dose of PK for PET studies resulted in a total EDE of 3.94 mSv for children aged 4–7 y, 4.32 mSv for children aged 8–12 y, and 5.13 mSv for adolescents (aged 13–17 y). In comparison, the total EDE to the adults was 5.47 mSv.

FIGURE 2. Three sequential whole-body ^{11}C -(R)-PK11195 PET/CT scans showing time-dependent biodistribution of PK at 20 min after injection (A), 40 min after injection (B), and 60 min after injection (C). PK uptake was highest in gallbladder and urinary bladder, followed by liver, kidney, bone marrow, salivary gland, and heart wall, with minimal localization in all other organs including normal brain and lungs.

The gallbladder received the maximum radiation dose in the 2 youngest pediatric groups, whereas the urinary bladder received the highest radiation in adolescents and adults. No effect of sex was found on the residence times or on the EDE values.

FIGURE 3. Decay-corrected (A) and non-decay-corrected (B) time-activity curves for kidneys, liver, brain, urinary bladder, and gallbladder in 5-y-old subject. Tracer activity in brain reached maximum within first 2 min and then decreased exponentially (inset of A). Non-decay-corrected time-activity curves were extrapolated to 240 min (12 half-lives), applying only physical decay of tracer (inset of B).

DISCUSSION

The results of our study suggest that the radiation dose from PK PET is comparable to doses from other clinically used ^{11}C -labeled PET tracers. Specifically, 17 MBq/kg of administered activity of PK resulted in good image quality and a total effective dose of about or less than 5 mSv for all age groups.

A rapid increase in PK uptake in the normal brain followed by rapid clearance suggested the free passage of PK through the intact blood-brain barrier but a relatively low level of PBRs in the brain, consistent with previous findings (9,10). In the body, PK uptake was mostly concentrated in the gallbladder, urinary bladder, liver, kidneys, and bone marrow. In humans, ^{11}C -PK11195 is metabolized into 2 main radioactive metabolites— ^{11}C -formaldehyde and ^{11}C -*N*-methyl-sec-butylamine (11,12)—which may contribute to the high liver and gallbladder uptake. PK binding to PBRs located on hepatocytes and biliary epithelial tissue may also contribute to the liver and gallbladder tracer uptake. Salivary gland and heart wall also showed a relatively high PK uptake. Although microarray data show the highest expression of PBRs in the lung (13,14), the lung showed low PK localization. The local formation of $^{11}\text{CO}_2$ from ^{11}C -PK11195 through decarboxylation and its rapid elimination may be the possible reason for low uptake in the lungs (15). We did not find high activity in the adrenal glands, ovaries and testes, and other organs with previously

reported high PBR uptake (16). The reason could be a combination of partial-volume effects because of the small size of these organs and their proximity to larger organs with high PK uptake, such as the liver, kidneys, and urinary bladder. Highest PK uptake was determined in the gallbladder, which is consistent with reports that the highest activity of ^{123}I -iodo-PK11195 was in the bile of dogs (17) and in adult volunteers (16). Sex analysis did not reveal any difference in the biodistribution or dosimetry between men and women.

The biodistribution and dosimetry of other PBR radio-ligands has been performed previously in animals (9, 18–23) and healthy adult human volunteers (16,18,24). Hashimoto et al. (21) studied the biodistribution of ^3H -PK 11195 in mice and found high accumulations of radioactivity in the heart, lung, spleen, kidneys, and adrenals. In ex vivo rat biodistribution and inhibition studies, the fluoromethyl derivative of 2-quinolinecarboxamide (a PBR radio-ligand) rapidly accumulated in PBR-rich tissues such as the heart, lung, kidneys, spleen, and adrenals and at a lower level in the brain, which was further confirmed by PET (19). Radiation doses of ^{11}C -PBR28, based on biodistribution data in monkeys and humans, showed that the highest organ doses were received by kidneys, spleen, and lungs, with an overall effective dose of 6.6 $\mu\text{Sv/MBq}$ (18), similar to that reported in the present study. Moreover, low uptake of ^{11}C -PBR28 was reported in the brain of healthy human subjects, compared with monkeys (24). In human SPECT

TABLE 1. Mean Residence Times (Hours) Obtained from PET

Organ	Children 4–7 y	Children 8–12 y	Children 13–17 y	Adults
Gallbladder	0.002 (47)	0.003 (52)	0.002 (44)	0.002 (59)
Urinary bladder	0.005 (68)	0.007 (61)	0.010 (55)	0.014 (71)
Liver	0.025 (21)	0.025 (36)	0.024 (27)	0.031 (20)
Kidneys	0.007 (55)	0.007 (43)	0.003 (12)	0.011 (18)
Marrow	0.012 (31)	0.013 (11)	0.016 (16)	0.022 (33)
Brain	0.016 (22)	0.011 (23)	0.006 (34)	0.005 (14)
Lungs	0.003 (21)	0.002 (30)	0.002 (27)	0.003 (33)
Heart	0.002 (27)	0.002 (38)	0.003 (42)	0.006 (41)

Coefficient of variation (COV% = $[\text{SD}/\text{mean}] \times 100\%$) is given in parentheses.

TABLE 2. Radiation Doses for ^{11}C -(*R*)-PK11195 in Children and Adults

Target organ	Organ dose ($\mu\text{Sv}/\text{MBq}$)			
	Children 4–7 y	Children 8–12 y	Children 13–17 y	Adults
Adrenals	9.8 ± 0.4	6.2 ± 0.1	3.9 ± 0.1	3.2 ± 0.1
Brain	5.3 ± 1.3 (8)	3.5 ± 1.0 (9)	2.1 ± 0.7 (5)	1.7 ± 0.5 (7)
Breast	7.1 ± 0.3	4.4 ± 0.2	2.9 ± 0.1	2.1 ± 0.1
Gallbladder wall	21.5 ± 12.9 (6)	17.3 ± 8.9 (6)	9.7 ± 5.1 (3)	8.0 ± 2.3 (3)
LL intestine	9.3 ± 1.0	5.9 ± 0.6	3.8 ± 0.4	3.1 ± 0.2
Small intestine	9.9 ± 0.9	6.3 ± 0.5	4.0 ± 0.3	3.1 ± 0.3
Stomach	9.0 ± 0.6 (6)	5.7 ± 0.2 (7)	3.6 ± 0.2 (3)	2.9 ± 0.1 (3)
UL intestine	9.7 ± 1.1	6.1 ± 0.7	3.8 ± 0.4	3.1 ± 0.3
Heart wall	10.9 ± 1.3 (6)	7.0 ± 1.0 (7)	5.1 ± 0.7 (2)	4.4 ± 0.6 (3)
Kidneys	18.5 ± 8.2 (6)	13.5 ± 7.0 (6)	5.4 ± 2.6 (3)	11.4 ± 4.9 (3)
Liver	15.2 ± 4.8 (6)	10.3 ± 4.2 (7)	6.7 ± 2.2 (3)	6.2 ± 3.1 (4)
Lungs	5.9 ± 1.1 (6)	3.9 ± 0.6 (6)	2.7 ± 0.4 (3)	2.0 ± 0.4 (2)
Muscle	8.3 ± 0.2	5.2 ± 0.1	3.3 ± 0.1	2.5 ± 0.1
Ovaries	9.9 ± 1.8	6.2 ± 1.2	4.1 ± 0.8	3.2 ± 0.7
Pancreas	10.1 ± 0.2	6.5 ± 0.1	4.0 ± 0.1	3.2 ± 0.1
Red marrow	12.1 ± 2.4	7.1 ± 0.4	4.8 ± 0.9	4.5 ± 0.3
Osteogenic cells	13.3 ± 2.8	8.7 ± 1.8	6.2 ± 1.4	4.9 ± 1.1
Skin	7.0 ± 0.2	4.2 ± 0.1	2.6 ± 0.1	2.0 ± 0.1
Spleen	9.3 ± 0.3	5.7 ± 0.2	3.6 ± 0.1	2.8 ± 0.1
Testes	8.1 ± 1.5	5.1 ± 1.0	3.4 ± 0.8	2.5 ± 0.5
Thymus	8.4 ± 0.4	5.3 ± 0.2	3.4 ± 0.2	2.6 ± 0.1
Thyroid	8.9 ± 0.3	5.4 ± 0.1	3.4 ± 0.1	2.5 ± 0.1
Urinary bladder wall	20.8 ± 6.7 (2)	13.8 ± 4.1 (2)	17.5 ± 3.3 (2)	12.0 ± 3.5 (2)
Uterus	10.1 ± 0.8	6.4 ± 0.4	4.4 ± 0.3	3.4 ± 0.3
Total body	9.0 ± 0.3	5.6 ± 0.2	3.5 ± 0.1	2.8 ± 0.1

Values are given as mean $\pm$ SD (number of observation).
LL intestine = lower large intestine; UL intestine = upper large intestine.

studies, ^{123}I -iodo-PK11195 was rapidly cleared from the blood, mainly by the hepatobiliary system; approximately 20% was excreted in urine by 48 h in healthy adults (16). The effective dose was $40.3 \mu\text{Sv}/\text{MBq}$ and the effective dose for the study was 7.46 mSv after an administration of 185 MBq of ^{123}I -iodo-PK11195. Recently, Roivainen et al. (15) studied the whole-body distribution and metabolism of ^{11}C -PK11195 in 10 patients with Alzheimer disease and 4 healthy adults. Similar to our findings, they reported high uptake in urinary bladder, liver, kidneys, vertebral column, heart, and salivary gland and low uptake in lungs and brain.

TABLE 3. ^{11}C -(*R*)-PK11195 Radiation Doses

Age group	EDE ($\mu\text{Sv}/\text{MBq}$)	Total EDE* (mSv)
Children 4–7 y (~20 kg)	11.6 (0.043)	3.94 (0.39)
Children 8–12 y (~33 kg)	7.7 (0.028)	4.32 (0.43)
Children 13–17 y (~57 kg)	5.3 (0.020)	5.13 (0.51)
Adults (in comparison)	4.6 (0.017)	5.47 (0.55)

*For injected activity of 17 MBq/kg (0.45 mCi/kg). Total EDE was calculated as EDE multiplied with age-appropriate injected activity (340 MBq for children 4–7 y, 560 MBq for children 8–12 y, and 970 MBq for children 13–17 y).

Data in parentheses are rem/mCi in EDE column and rem in Total EDE column.

An effective dose range of 4–14 $\mu\text{Sv}/\text{MBq}$ in adults has been reported for various ^{11}C tracers used for brain imaging including radioligands used for inflammation imaging (18). Therefore, the current results show that ^{11}C -(*R*)-PK11195 radiation doses are comparable to those of other radiotracers. Although children received a higher EDE per unit administered activity (i.e., mSv/MBq) than adults, the total EDE for the administered activity used (17 MBq/kg) was lower in children.

One of the limitations of the present study is that most of the children were taking some medications for their brain disorders, and these medications might have affected the kinetics and biodistribution of ^{11}C -PK11195. PBRs show a wide range of specificity for some organic compounds and drugs, such as dipyrindamole, disulfiram, lidocaine, pyrethroid insecticides, porphyrins, steroids, and lindane (the γ -isomer of the compound hexachlorocyclohexane) (25). The histidine-modifying reagent diethylpyrocarbonate also noncompetitively inhibits the binding of PK11195, observed in rats but not in bovine PBRs. Imidazopyridines and arylindoleamines also have subnanomolar affinity to PBRs. Another limitation is that all of the children were studied for brain disorders associated with neuroinflammation. It is not clear whether the actions of medications or possible systemic changes associated with their brain disorders might be responsible for the apparent differences in elimination of the tracer.

CONCLUSION

The present study shows that PK uptake is mostly concentrated in the gallbladder and urinary bladder, followed by the liver, kidney, bone marrow, salivary gland, and heart wall, with minimal localization in other organs including brain and lungs. Moreover, PK is excreted through both the hepatobiliary and the renal systems. At clinically practical administered activities, the radiation dose from ^{11}C -PK11195 in both children and adults is comparable to that from other clinical PET tracers and diagnostic radiopharmaceuticals in routine clinical use.

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